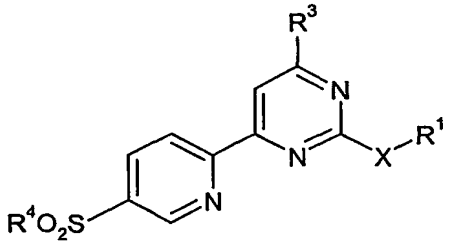
PYRIMIDINE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS

This invention relates to pyrimidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The enzyme cyclooxygenase (COX) has recently been discovered to exist in two isoforms, COX-1 and COX-2. COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. Prostaglandins generated by the action of COX have both physiological and pathological roles. It is generally believed that COX-1 is largely responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow. In contrast the inducible form, COX-2, is believed to be largely responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines. A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1. We have now found a novel group of compounds which are both potent and selective inhibitors of COX-2.

The invention thus provides a compound of formula (I)



(I)

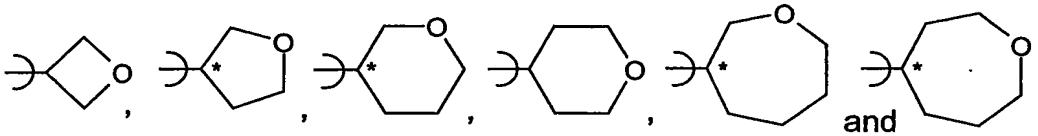
or a pharmaceutically acceptable salt thereof in which:

X is selected from the group consisting of oxygen or NR^2;

R^1 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, $A(CR^5R^6)_n$ and $B(CR^5R^6)_n$;

R^2 is selected from the group consisting of H and C_{1-6}alkyl;

R^3 is C_{1-2}alkyl substituted by one to five fluorine atoms;
R^4 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R^8CONH;
R^5 and R^6 are independently selected from H or C_{1-6}alkyl;
A is an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R^7;
R^7 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2;
B is selected from the group consisting of



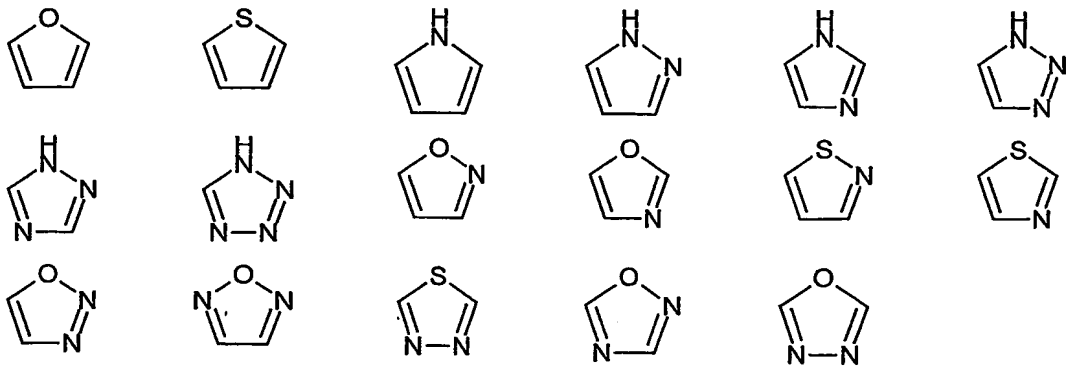
and where

) defines the point of attachment of the ring;
R^8 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl; and
n is 0 to 4.

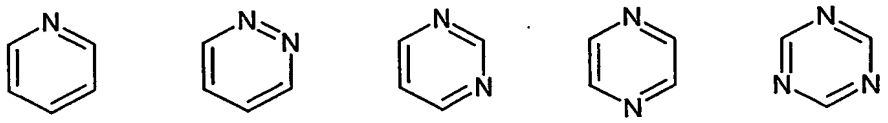
The term halogen is used to represent fluorine, chlorine, bromine or iodine.

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

The term 5-membered heteroaryl means a heteroaryl selected from the following:



The term 6- membered heteroaryl means a heteroaryl selected from the following:



The term 6-membered aryl means:

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures). In particular when the ring B lacks a plane of symmetry the compounds of formula (I) contain a chiral centre as indicated therein by the asterisk *. Furthermore, it will be appreciated by those skilled in the art that when R^5 and R^6 in formula (I) are different the corresponding compounds contain at least one chiral centre, by virtue of the asymmetric carbon atom defined thereby, and that such compounds exist in the form of a pair of optical isomers (i.e. enantiomers).

It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, **66**, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

In one aspect of the invention X is NR^2.

In another aspect of the invention R^1 is C_{5-7}cycloalkylC_{0-2}alkyl, C_{1-6}alkyl or $A(CR^5R^6)_n$.

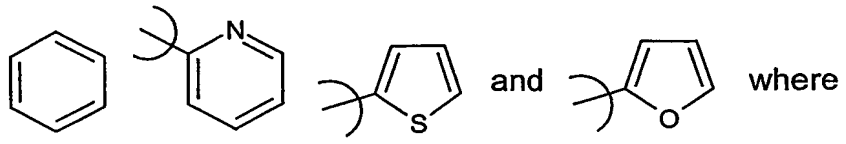
In another aspect of the invention R^2 is H or methyl.

In another aspect of the invention R^3 is CHF_2, CH_2F or CF_3. In another aspect R^3 is CF_3.

In another aspect of the invention R^4 is C_{1-6}alkyl, such as C_{1-3}alkyl (e.g. methyl).

In another aspect of the invention R^5 and R^6 are independently selected from H or methyl. In another aspect R^5 and R^6 are both H.

In another aspect of the invention A is selected from the group consisting of



) defines the point of attachment of the ring

and A is unsubstituted or substituted by one or two R^7.

In another aspect of the invention R^7 is selected from the group consisting of halogen (e.g. F), C_{1-3}alkyl (e.g. methyl), C_{1-3}alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3}alkoxy (e.g. methoxy).

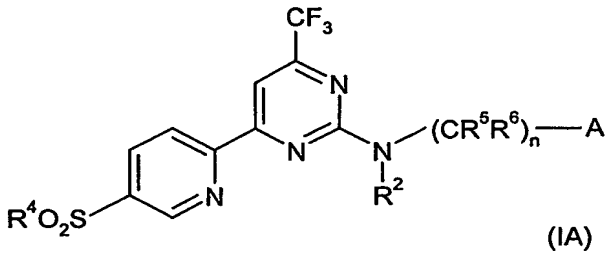
In another aspect of the invention R^8 is selected from the group consisting of C_{1-6}alkyl (e.g. ethyl), phenyl and aminomethyl.

In another aspect of the invention n is 0 to 2 (e.g. 1).

In another aspect of the invention X is NR^2; R^1 is $A(CR^5R^6)_n$; R^2 is selected from the group consisting of H and C_{1-6}alkyl; R^3 is CF_3; R^4 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R^8CONH; R^5 and R^6 are independently selected from H or C_{1-6}alkyl; A is C_{5-7}cycloalkyl or an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R^7; R^7 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2; R^8 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl; and n is 0 to 4.

It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

In a further aspect the invention provides a compound of formula (IA)



(IA)

and pharmaceutically acceptable salts thereof in which:

R^2 is selected from the group consisting of H and C_{1-6}alkyl;
R^4 is selected from the group consisting of C_{1-6}alkyl, NH_2 and R^8CONH;
R^5 and R^6 are independently selected from H or C_{1-6}alkyl;
A is C_{5-7}cycloalkyl or an unsubstituted 5- or 6-membered heteroaryl or an unsubstituted 6-membered aryl, or a 5- or 6-membered heteroaryl or a 6-membered aryl substituted by one or more R^7;
R^7 is selected from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one more fluorine atoms, C_{1-6}alkoxy, C_{1-6}alkoxy substituted by one or more F, NH_2SO_2 and C_{1-6}alkylSO_2;

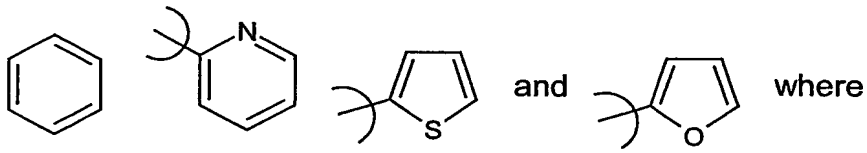
R^8 is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylOC_{1-6}alkyl, phenyl, HO_2CC_{1-6}alkyl, C_{1-6}alkyl$OCOC_{1-6}$alkyl, C_{1-6}alkylOCO, H_2NC_{1-6}alkyl, C_{1-6}alkyl$OCONHC_{1-6}$alkyl and C_{1-6}alkyl$CONHC_{1-6}$alkyl; and
n is 0 to 4.

In one aspect of the invention relating to compounds of formula (IA), R^2 is H or methyl.

In another aspect of the invention R^4 is C_{1-3}alkyl (e.g. methyl).

In another aspect of the invention R^5 and R^6 are independently selected from H or methyl. In another aspect R^5 and R^6 are both H.

In another aspect of the invention A is selected from the group consisting of C_{5-7}cycloalkyl or



where

) defines the point of attachment of the ring
and A is unsubstituted or substituted by one or two R^7.

In another aspect of the invention R^7 is selected from the group consisting of halogen (e.g. F), C_{1-3}alkyl (e.g. methyl), C_{1-3}alkyl substituted by one to three fluorine atoms (e.g. CF_3), and C_{1-3}alkoxy (e.g. methoxy).

In another aspect of the invention R^8 is selected from the group consisting of C_{1-6}alkyl (e.g. ethyl), phenyl and aminomethyl.

In another aspect of the invention n is 0 to 2 (e.g. 1).

It is to be understood that the invention covers all combinations of particular aspects of the invention as described hereinabove.

In a preferred aspect the invention provides the following compounds:
[4-(5-Methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidin-2-yl]-methyl-(6-methyl-pyridin-2-ylmethyl)-amine,

Benzyl-[4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidin-2-yl]-amine,
Cyclohexyl-[4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidin-2-yl]-amine.

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compound of formula (I) may be used for preparing the more pure forms used in pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are available in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrysallised from organic solvents, solvent of recrystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all the polymorphic forms of the compounds of formula (I).

Compounds of the invention are potent and selective inhibitors of COX-2. This activity is illustrated by their ability to selectively inhibit COX-2 over COX-1.

In view of their selective COX-2 inhibitory activity, the compounds of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of the pain (both chronic and acute), fever and inflammation of a variety of conditions and diseases mediated by COX-2. Such conditions and diseases are well known in the art and include rheumatic fever; symptoms

associated with influenza or other viral infections, such as the common cold; lower back and neck pain; headache; toothache; sprains and strains; myositis; sympathetically maintained pain; synovitis; arthritis, including rheumatoid arthritis; degenerative joint diseases, including osteoarthritis; gout and ankylosing spondylitis; tendinitis; bursitis; skin related conditions, such as psoriasis, eczema, burns and dermatitis; injuries, such as sports injuries and those arising from surgical and dental procedures.

The compounds of the invention are also useful for the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; neuralgia, such as post-herpetic neuralgia and trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of the invention are also useful for the treatment of other conditions mediated by COX-2.

For example, the compounds of the invention inhibit cellular and neoplastic transformation and metastatic tumour growth and hence are useful in the treatment of certain cancerous diseases, such as colonic cancer and prostate cancer. The compounds of the invention are also useful in reducing the number

of adenomatous colorectal polyps and thus reduce the risk of developing colon cancer. The compounds of the invention are also useful in the treatment of cancer associated with overexpression of HER-2/neu, in particular breast cancer.

Compounds of the invention also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore are of use in the treatment of stroke; epilepsy; and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures).

Compounds of the invention also inhibit prostanoid-induced smooth muscle contraction and hence are of use in the treatment of dysmenorrhoea and premature labour.

Compounds of the invention are also useful in the treatment of liver disease, such as inflammatory liver disease, for example chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury, primary biliary cirrhosis, autoimmune hepatitis, nonalcoholic steatohepatitis and liver transplant rejection.

Compounds of the invention inhibit inflammatory processes and therefore are of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome; gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis; and the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia.

Compounds of the invention are also useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue.

Compounds of the invention are also useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space

occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

Compounds of the invention are also useful in the treatment of disorders ameliorated by a gastroprokinetic agent. Disorders ameliorated by gastroprokinetic agents include ileus, for example post-operative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); gastroparesis, such as diabetic gastroparesis; and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP).

According to a further aspect of the invention, we provide a compound of formula (I) for use in human or veterinary medicine.

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by COX-2 which comprises administering to said subject an effective amount of a compound of formula (I).

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I).

According to another aspect of the invention, we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by COX-2.

According to another aspect of the invention, we provide the use of a compound of formula (I) for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents. Examples of suitable agents for adjunctive therapy include a $5HT_1$ agonist, such as a triptan (e.g. sumatriptan or naratriptan); an adenosine A1 agonist; an EP ligand; an NMDA modulator, such as a glycine antagonist; a sodium channel blocker (e.g. lamotrigine); a substance P antagonist (e.g. an NK_1 antagonist); a cannabinoid; acetaminophen or phenacetin; a 5-lipoxygenase inhibitor; a leukotriene receptor antagonist; a DMARD (e.g. methotrexate); gabapentin and related compounds; a tricyclic antidepressant (e.g. amitryptilline); a neurone stabilising antiepileptic drug; a mono-aminergic uptake inhibitor (e.g. venlafaxine); a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor, such as an iNOS or an nNOS inhibitor; an inhibitor of the release, or action, of tumour necrosis factor α; an antibody therapy, such as a monoclonal antibody therapy; an antiviral agent, such as a nucleoside inhibitor (e.g. lamivudine) or an immune system modulator (e.g. interferon); an opioid analgesic; a local anaesthetic; a stimulant, including caffeine; an H_2-antagonist (e.g. ranitidine); a proton pump inhibitor (e.g. omeprazole); an antacid (e.g. aluminium or magnesium hydroxide; an antiflatulent (e.g. simethicone); a decongestant (e.g. phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine); an antitussive (e.g. codeine, hydrocodone, carmiphen, carbetapentane, or dextramethorphan); a diuretic; or a sedating or non-sedating antihistamine. It is to be understood that the present invention covers the use of a compound of formula (I) in combination with one or more other therapeutic agents.

The compounds of formula (I) are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) adapted for use in human or veterinary medicine. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

The compounds of formula (I) may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may

be in a form such that it can effect controlled release of the compounds of formula (I).

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative.

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) together with a further therapeutic agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically

acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

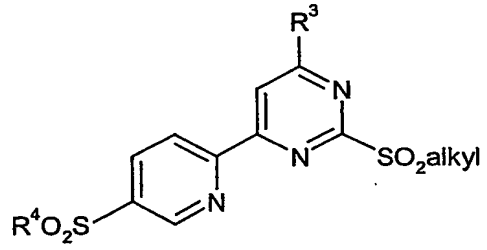
When a compound of formula (I) is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A proposed daily dosage of a compound of formula (I) for the treatment of man is 0.01mg/kg to 500mg/kg, such as 0.05mg/kg to 100mg/kg, e.g. 0.1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses. The precise dose employed will depend on the age and condition of the patient and on the route of administration. Thus, for example, a daily dose of 0.25mg/kg to 10mg/kg may be suitable for systemic administration.

Compounds of formula (I) may be prepared by any method known in the art for the preparation of compounds of analogous structure.

Compounds of formula (I) may be prepared by a process which comprises:

reacting a compound R^1XH of formula (II) or a protected derivative thereof with a compound of formula (III)

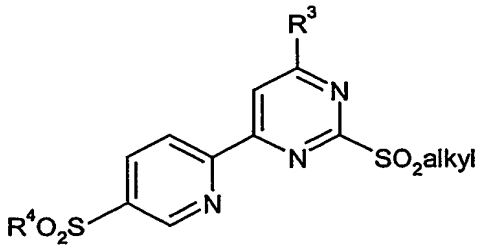


(III)

and thereafter and if necessary, interconverting a compound of formula (I) into another compound of formula (I); and/or deprotecting a protected derivative of compound of formula (I).

Compounds of formula (IA) may be prepared by a process which comprises:

reacting an amine $HNR^2(CR^5R^6)_nA$ of formula (IIA) or a protected derivative thereof with a compound of formula (III) wherein R^3 is CF_3



(III)

and thereafter and if necessary, interconverting a compound of formula (IA) into another compound of formula (IA); and/or deprotecting a protected derivative of compound of formula (IA).

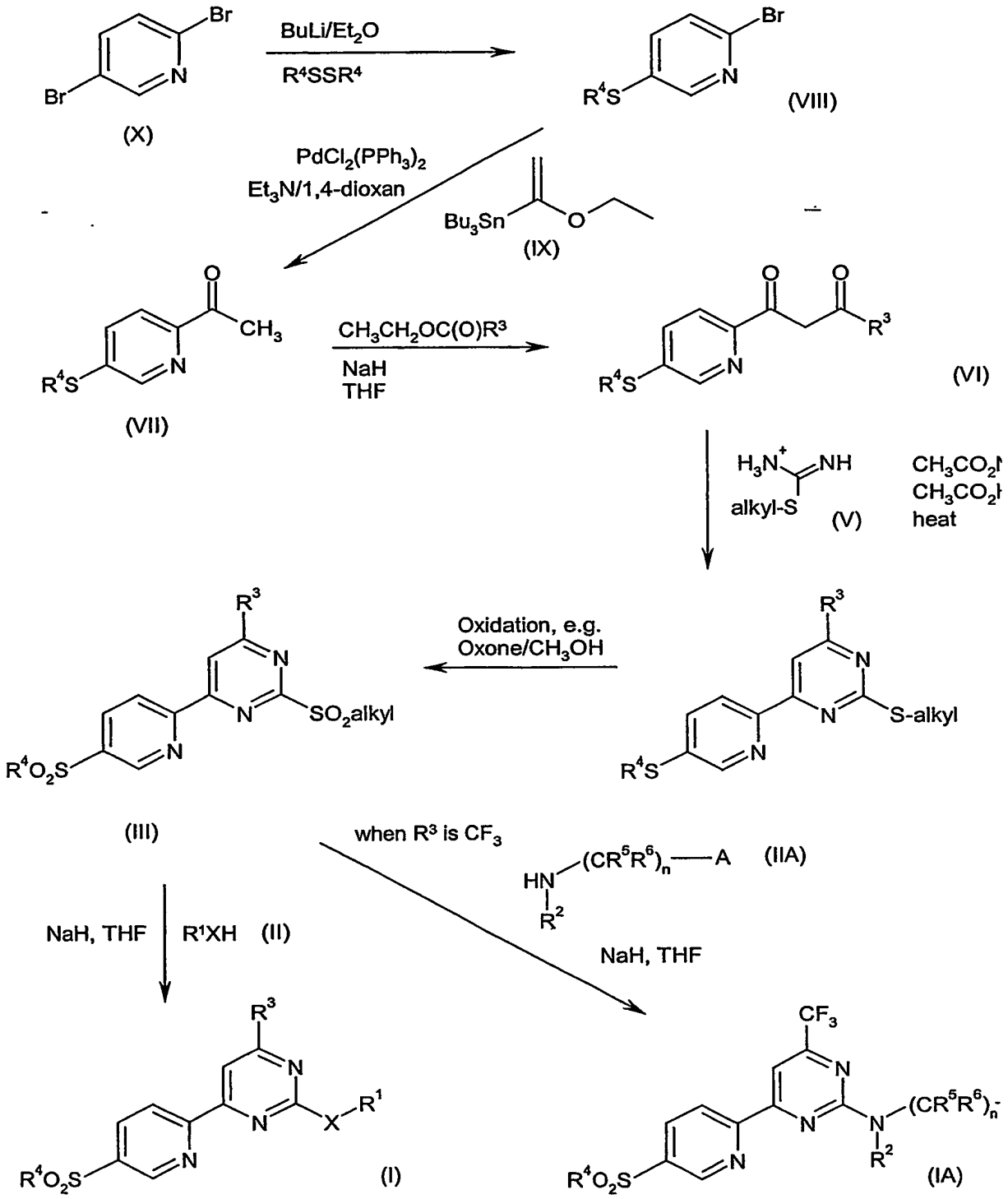
The overall synthesis of a compound of formula (I) or (IA) is shown in Scheme 1 below in which X, R^1 and R^3 are as defined in formula (I) above unless otherwise stated and R^4 is C_{1-6}alkyl; THF is tetrahydrofuran; MTBE is methyl t-butyl ether; and alkyl is a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group.

Referring to Scheme 1, when X=O, compounds of formula (I) may conveniently be prepared by the treatment of compounds of formula (III) with an alcohol of formula (II) in the presence of sodium hydride. The reaction is conveniently carried out in a solvent such as THF and at between ambient temperature and reflux.

Referring to Scheme 1, when $X=NR^2$, compounds of formula (I) may be prepared via the treatment of compounds of formula (III) with an amine of formula (II). This is conveniently carried out in a solvent, such as a nitrile (e.g. methylnitrile) and at elevated temperature (e.g from about 50°C to reflux). An excess of the amine may be used in place of the solvent.

Alternatively, the treatment of compounds of formula (III) with an amine of formula (II) is conveniently carried out in a solvent, such as a teriary amine (e.g. NMP) and at elevated temperature (e.g. from 120°C to 250°C) and with or without microwave irradiation.

Scheme 1


BuLi/Et2O
R4SSR4
(X)
(VIII)
PdCl2(PPh3)2
Et3N/1,4-dioxan
Bu3Sn
(IX)
(VII)
CH3CH2OC(O)R3
NaH
THF
(VI)
(V)
heat
Oxidation, e.g.
Oxone/CH3OH
SO2alkyl
S-alkyl
(III)
when R3 is CF3
(IIA)
NaH, THF
R1XH (II)
NaH, THF
(I)
(IA)

Conveniently the oxidation shown in Scheme 1 is effected using a monopersulfate compound, such as potassium peroxymonosulfate (known as Oxone™) and the reaction is carried out in a solvent, such as an aqueous alcohol, (e.g. aqueous methanol), and at between -78°C and ambient temperature.

Alternatively, the oxidation shown in Scheme 1 may be effected using hydrogen peroxide in the presence of catalytic sodium tungstate dihydrate. The reaction may be carried out in a solvent such as acetic acid and at between ambient temperature and reflux (e.g. 50°C).

Referring to Scheme 1, the cyclisation of diones of formula (VI) to give the corresponding pyrimidines of formula (IV) is conveniently carried out employing a thioronium salt such as a 2-methyl-2-thiopseudourea sulfate and under reflux.

Compounds of formula (VI) may be readily prepared from acetophenones of formula (VII) via treatment with ethyl trifluoroacetate (Aldrich) in the presence of sodium hydride. The reaction is conveniently carried out in a suitable solvent such as tetrahydrofuran at a temperature between 0°C and reflux.

Acylation of compounds of formula (VIII) to give compounds of formula (VII) can be conveniently achieved by treatment with the compound of formula (IX) in the presence of triethylamine and a catalytic quantity of dichlorobis(triphenylphoshine) palladium (II). The reaction is suitably performed in a solvent such as 1,4-dioxan at a temperature between ambient and reflux.

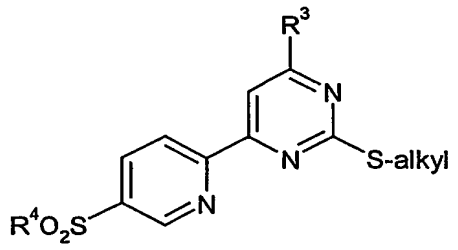
Alternatively, the acylation of compounds of formula (VIII) to give compounds of formula (VII) can be achieved via the treatment of (VIII) with excess *tert*-butyllithium in THF at low temperature, such as -78°C, followed by the addition of a suitable acylating agent such as dimethyl acetamide or N-methoxy-N-methyl acetamide.

Preparation of compounds of formula VIII may conveniently be achieved via treatment of compounds of formula X with butyllithium at low temperature, such as -78°C, followed by the addition of the appropriate disulfide. The reaction is conveniently carried out in a suitable solvent such as diethyl ether at a temperature between -78°C and ambient temperature.

It will be appreciated by those skilled in the art that certain of the procedures described in Scheme 1 for the preparation of compounds of formula (I) or intermediates thereto may not be applicable to some of the possible substituents.

It will be further appreciated by those skilled in the art that it may be necessary or desirable to carry out the transformations described in Scheme 1 in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I).

In one variation of Scheme 1, compounds of formula (III) wherein R^4 is C_{1-6}alkyl or NH_2 may be prepared by oxidising a compound of formula (IV)A:



(IV)A

under oxidation conditions described hereinabove. Compounds of formula (IV)A may be prepared according to the general procedures of Scheme 1 by employing sulphonyl derivatives in place of the corresponding sulfide compounds of formulae (VI), (VII) and (VIII) . In this instance the sulfonyl derivative of a compound of formula (VIII) may be prepared via oxidation of (VIII) using standard techniques, such as those described hereinabove.

It will be appreciated by those skilled in the art that compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors. Suitable interconversions, such as alkylations, are well known to those skilled in the art and are described in many standard organic chemistry texts, such as 'Advanced Organic Chemistry' by Jerry March, fourth edition (Wiley, 1992), incorporated herein by reference. For example, compounds of formula (I) wherein R^1 is C_{1-6}alkyl, C_{1-2}alkyl substituted by one to five fluorine atoms, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-10}cycloalkylC_{0-6}alkyl, C_{4-12}bridged cycloalkyl, $A(CR^5R^6)_n$ and $B(CR^5R^6)_n$ (with the proviso that n is not zero) may be prepared by alkylating the corresponding compound of formula (I) wherein R^1 is H.

Acylation of compounds of formula (I) wherein R^4 is NH_2, to provide compounds of formula (I) wherein R^4 is $NHCOR^6$, may be carried out by conventional means, for example by employing conventional acylating agents such as those described in 'Advanced Organic Chemistry', pp 417-424, incorporated herein by reference.

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions. The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green and Peter G M Wuts, second edition, (John Wiley and Sons, 1991), incorporated herein by reference, which also describes methods for the removal of such groups.

Amines of formula (II) are either known compounds or may be prepared by literature methods, such as those described in 'Comprehensive Organic Transformations: a guide to functional group preparations' by Richard Larock (VCH, 1989), incorporated herein by reference.

Thioronium salts of formula (V) are either known compounds or may be prepared by literature methods, such as those described in A H Owens *et al*, Eur J Med Chem, 1988, 23(3), 295-300, incorporated herein by reference

Compounds (IX) and (X) are commercially available.

Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention. Compounds of formulae (III) and (IV) are key intermediates and represent a particular aspect of the present invention.

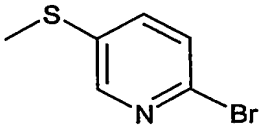
Solvates (e.g. hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps.

The Intermediates and Examples that follow illustrate the invention but do not limit the invention in any way. All temperatures are in ^0C. Flash column chromatography was carried out using Merck 9385 silica. Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond

Elut (Si) cartridges (Anachem) under 15mmHg vacuum. Thin layer chromatography (Tlc) was carried out on silica plates. In addition to those already defined, the following abbreviations are used: Me, methyl; Ac, acyl; DMSO, dimethylsulphoxide; TFA, trifluoroacetic acid; DME, dimethoxyethane; DCM, dichloromethane; NMP, N- methyl pyrrolidone; and MTBE, methyl t-butyl ether.

Intermediate 1

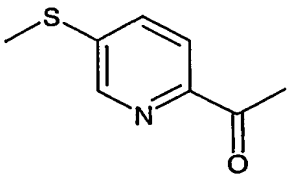
2-Bromo 5-methylsulfanyl pyridine



A stirring suspension of 2,5-dibromopyridine (10g, 0.042mol) in anhydrous diethyl ether (240mL) was cooled to -78°C under nitrogen before the dropwise addition of n-butyl lithium (1.6M in hexanes, 0.044mol, 27.5mL). The reaction was stirred at -78°C for 4 hours before the dropwise addition of methyl disulphide (0.044mol, 3.91mL). The reaction was allowed to warm to 22°C and stirred for a further 18 hours. The reaction was quenched with water (100mL) and the aqueous and organic layers partitioned. The aqueous layer was extracted with diethyl ether (x3). The extracts were combined with the organic layer, washed with brine, dried ($MgSO_4$) and the solvent removed. The crude product was purified by crystallisation from diethyl ether at -20°C to afford the title compound as a white solid: ^1H NMR ($CDCl_3$) - δ2.50 (s, 3H), 7.38 (dd, 1H), 7.42 (dd, 1H), 8.23 (d,1H).

Intermediate 2

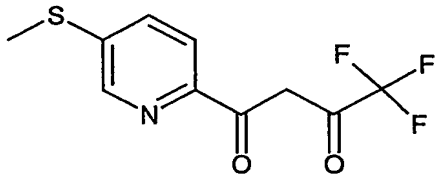
1-(5-Methylsulfanyl-pyridin-2-yl)-ethanone



To a stirring solution of 2-bromo 5-methylsulfanyl pyridine (3.05g 14.9mmol), triethylamine (2.10mL, 14.9mmol) and (1-ethoxyvinyl) tributyl tin (10.1mL, 29.8mmol) in anhydrous 1,4-dioxane (100mL), was added dichlorobis(triphenylphosphine) palladium (II) (5mol%, 0.524g) and the reaction heated to reflux under nitrogen for 18 hours. After cooling, dichlorobis(triphenylphosphine) palladium (II) was added and the reaction heated under nitrogen for a further 18 hours. The reaction was allowed to cool and the reaction mixture partitioned between saturated aqueous potassium fluoride solution (250mL) and diethyl ether (250mL). The ether layer was separated and 2N hydrochloric acid (250mL) added. The acid layer was separated and sodium carbonate added portionwise until the solution reached pH 8. The solution was extracted with dichloromethane (3 x 200mL). The organic extracts were combined and the solvent removed. The residue was partitioned between cyclohexane (60ml) and acetonitrile (60mL). The acetonitrile layer was separated and the solvent removed to yield a brown solid. The crude product was purified by flash column chromatography (cyclohexane:ethyl acetate, 95:5) to afford the title compound as a white solid: ^{1}H NMR ($CDCl_3$) - δ2.56 (s, 3H), 2.69 (s, 3H), 7.60 (dd, 1H), 7.96 (d, 1H), 8.49 (d, 1H).

Intermediate 3

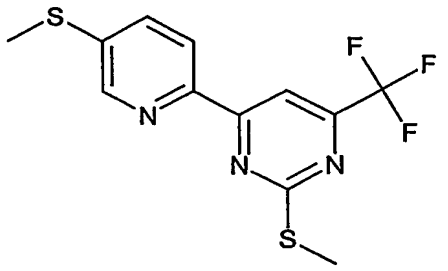
4,4,4-Trifluoro-1-(5-methylsulfanyl-pyridin-2-yl)-butane-1,3-dione



A stirring solution of sodium hydride (0.253g, 6.31mmol) in anhydrous tetrahydrofuran (20mL) was cooled under nitrogen to 0°C before the addition of 1-(5-methylsulfanyl-pyridin-2-yl)-ethanone (0.880g, 5.26mmol) in anhydrous tetrahydrofuran (20mL). Ethyl trifluoroacetate (0.751mL, 6.31mmol) was added dropwise and the reaction allowed to rise in temperature to 22°C, then heated to reflux and stirred under nitrogen for 17 hours. The solvent was removed and the residue partitioned between saturated aqueous ammonium chloride (10mL) and dichloromethane (10mL). The aqueous layer was separated and extracted with

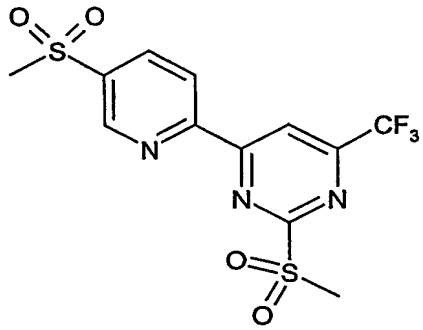
DCM (x3). The organic layers were combined, dried and the solvent removed to yield the title compound: MS m/z 264 (M+1).

Intermediate 4
2-Methylsulfanyl-4-(5-methylsulfanyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine



To a solution of 4,4,4-trifluoro-1-(5-methylsulfanyl-pyridin-2-yl)-butane-1,3-dione (0.600g, 2.28mmol) in glacial acetic acid (6mL) was added 2-methyl 2-thiopseudourea sulphate (0.761g, 2.74mmol) and sodium acetate (0.224g, 2.74mmol). The reaction was heated to 120°C under nitrogen for 21 hours. The reaction was allowed to cool before the addition of water (10mL), leading to precipitation of a solid. The reaction mixture was poured onto water (10mL) and stirred for 15 minutes at 22°C. The precipitate was filtered from the aqueous solution, washed with water, and dried *in vacuo* to yield the title compound as a grey solid: MS m/z 317 (M+1).

Intermediate 5
2-Methanesulfonyl-4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine

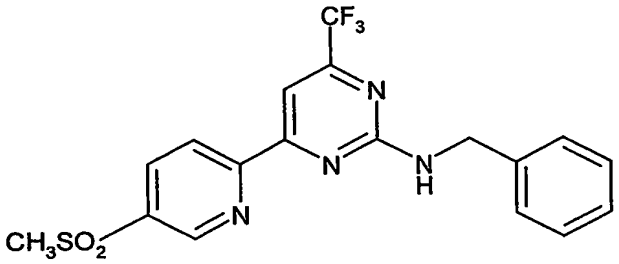


To a stirring solution of 2-methylsulfanyl-4-(5-methylsulfanyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine (0.617g, 1.94 mmol) in methanol (50mL) was added a solution of oxone (4.89g, 7.95mmol) in water (50mL). The suspension was

stirred at 22°C for 19 hours. Methanol was removed *in vacuo* and the aqueous suspension extracted with ethyl acetate (3 x 50mL). The organic extracts were combined, dried ($MgSO_4$) and the solvents removed *in vacuo* to yield the title compound as a white solid. MS m/z 382 (M+1).

Example 1

Benzyl-[4-(5-methanesulfonyl-pyridin-2-yl)-6-methyl-pyrimidin-2-yl-amine

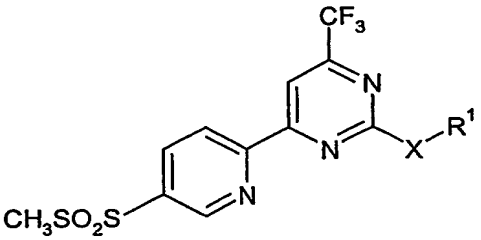


To a solution of 2-methanesulfonyl-4-(5-methanesulfonyl-pyridin-2-yl)-6-trifluoromethyl-pyrimidine (30mg, 0.0787mmol) in anhydrous N-methyl pyrrolidinone (1.5mL) was added benzylamine (0.157mmol, 17μL). The reaction was stirred at 22°C for 17 hours. The solvent was removed from the reaction (Genevac vacuum centrifuge) and the residue purified using a 1g silica solid phase extraction cartridge (gradient elution - dichloromethane:cyclohexane 1:1 to dichloromethane) to yield the title compound as a cream coloured solid: LC-MS retention time : 3.68 min. MS m/z 409 (M+1)

Examples 2 to 13

- Examples 2 to 13, as shown in Table 1 that follows, were prepared in the manner described for Example 1.

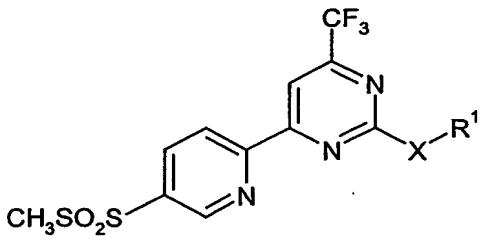
Table 1



(I)

Ex	R^1	X	MS
2	2-pyridinemethyl	NH	MH+ 410

Table 1



(I)

Ex	R^1	X	MS
3	2-(6-methylpyridine)methyl	NCH_3	MH+ 438
4	2-(5-methylfuran)methyl	NH	MH+ 413
5	cyclohexyl	NH	MH+ 401
6	cyclohexyl	NCH_3	MH+ 415
7	2-furylmethyl	NH	MH+ 399
8	2-thiophenylmethyl	NH	MH+ 415
9	2-furylmethyl	NCH_3	MH+ 413
10	4-chlorobenzyl	NH	MH+ 444
11	cyclopentyl	NH	MH+ 387
12	benzyl	NCH_3	MH+ 423
13	4-methylbenzyl	NH	MH+ 423

Biological Data

Microsomal Assay

Inhibitory activity against microsomal h-COX2 was assessed against a microsomal preparation from baculovirus infected SF9 cells. An aliquot of microsomal preparation was thawed slowly on ice and a 1/40,000 dilution prepared from it into the assay buffer (sterile water, degassed with argon containing 100mM HEPES (pH 7.4), 10mM EDTA (pH7.4), 1mM phenol, 1mM reduced glutathione, 20mg/ml gelatin and 0.001mM Hematin). Once diluted the enzyme solution was then sonicated for 5 seconds (Branson sonicator, setting 4, 1cm tip) to ensure a homogeneous suspension. 155µl enzyme solution was

then added to each well of a 96-well microtitre plate containing either 5µl test compound (40x required test concentration) or 5µl DMSO for controls. Plates were then mixed and incubated at room temperature for 1 hour. Following the incubation period, 40µl of 0.5µM arachidonic acid was added to each well to give a final concentration of 0.1µM. Plates were then mixed and incubated for exactly 10 minutes (room temperature) prior to addition of 25µl 1M HCl (hydrochloric acid) to each well to stop the reaction. 25µl of 1M NaOH (sodium hydroxide) was then added to each well to neutralise the solution prior to determination of PGE_2 levels by enzyme immunoassay (EIA).

The following IC_{50} values for inhibition of COX-2 and COX-1 were obtained from the microsomal assay for compounds of the invention:

Example No.	COX-2: IC_{50}(µM)	COX-1: IC_{50}(µM)
1	0.051	23.1
2	0.542	nt
3	0.005	67.1
4	0.218	>100
5	0.019	>100
6	0.077	26.3
7	0.748	46.8
8	0.04	nt
9	0.072	>100
10	0.354	90.2
11	0.433	>96.1
12	0.001	>100
13	0.193	>100